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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,630	08/05/2003	Klaus Giese	39078-0005	6369

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,630'	GIESE ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,15-17,19,29,31,32 and 34-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,15-17,19,29,31,32 and 34-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/07/2007 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 09/07/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 06/13/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 09/07/2007 claims 12-13, 15-17, 19, 29, 31-32 and 34-62 are pending and currently under examination. Applicant has canceled claims 1-11, 14, 18, 20-28, 30 and 33.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 11/12/2007 is in compliance with 37 CFR 19.7. The information disclosure statements has been considered by the examiner and signed copies have been placed in the file.

Claim Objections

Claim 34 is objected to because of the following informalities: The claim recites "said molecules" when the claim is only drawn to a single double stranded ribonucleic acid molecule. Appropriate correction is required.

Claim 38 is objected to because of the following informalities: The claim recites "each stretch is 18-23 base pairs long". The use of the phrase "base pairs" is inconsistent with the context of the claim because a stretch in the claim is referring to an individual strand of nucleotides. Changing "base pairs" to "nucleotides", for example, would obviate this rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 29 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the dsRNA molecule of claims 34 and 44 in a pharmaceutically acceptable carrier or diluent, does not reasonably provide enablement for mediating RNAi via introducing dsRNA molecules and a resultant treatment effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, the language "pharmaceutical composition" in claims 29 and 41 implies a therapeutic or treatment benefit that is not enabled. The *in vivo* inhibition and treatment effects described in the specification involve prophetic examples only and

have not been reduced to practice. Amendment of the claims to read "A composition comprising the dsRNA molecule of claims 34 or 44 and a pharmaceutically acceptable carrier or diluent", for example, would obviate this rejection.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The instant invention is drawn to a pharmaceutical composition comprising the siRNA molecule of claim 1 in an acceptable carrier or diluent.

There is no guidance in the specification as filed that teaches how to mediate RNA interference and a resultant treatment effect *in vivo*. Applicant is not enabled for mediating RNA interference *in vivo* with the instantly recited pharmaceutical composition, as delivery is known in the art to be unpredictable with regards to dsRNA duplexes.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using dsRNA. Scherer et al. (Nat. Biotechnol., 2003, 21(12), pages 1457-

1465) teach that antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi) each face remarkably similar problems for effective application: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. Scherer et al. teach that these challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent.

Mahato et al. (Expert Opinion on Drug Delivery, January 2005, Vol. 2, No. 1, pages 3-28) teach that antisense oligodeoxynucleotides and double-stranded small interfering RNAs have great potential for the treatment of many severe and debilitating diseases. Mahato et al. teach that efforts have made significant progress in turning these nucleic acid drugs into therapeutics, and there is already one FDA-approved antisense drug in the clinic. Mahato et al. teach that despite the success of one product and several other ongoing clinical trials, challenges still exist in their stability, cellular uptake, disposition, site-specific delivery and therapeutic efficacy. Mahato et al. teach that in order for siRNAs to be used as therapeutic molecules several problems have to be overcome, including: the selection of the best sequence-specific siRNA for the gene to be targeted and the ability to minimize degradation in the body fluids and tissues.

Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7) reviews the state of the art with regard to RNAi and has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical

issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

As outlined above, it is well known that there is a high level of unpredictability in the RNAi art for therapeutic *in vivo* therapeutic applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad method of mediating RNA interference encompassing *in vivo* treatment effects with the instantly recited pharmaceutical composition.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of RNA *in vivo* by the broadly disclosed methodologies of the instantly specification with the instantly claimed pharmaceutical composition would result in successful RNA interference and a therapeutic effect. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the molecule *in vivo*, delivery of the molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 recites the limitation "said first stretch" and "said second stretch". There is insufficient antecedent basis for this limitation in the claim because claim 34 from which claim 35 depends only refers to a stretch of nucleotides in each strand and does not identify each stretch as being a first or second stretch of nucleotides. For purposes of prior art and examination, the claim will be interpreted to mean the first strand comprises a first stretch and the second strand comprises a second stretch, which is consistent with language in the currently amended claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-13, 15-17, 19, 29, 31-32 and 34-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (of record, PTO 892 filed 01/12/2006) and Tuschl et al. (of record, PTO 892 filed 01/12/2006).

The instant claims are drawn to a double stranded ribonucleic acid molecule wherein the first strand is complementary to a target molecule, the second strand is complementary to a said first strand, wherein each strand comprises a stretch of alternating single 2'-modified and unmodified nucleotides. The claims are further drawn to a double stranded ribonucleic acid molecule comprising a first and second strand comprising a first and second stretch of nucleotides wherein each stretch consists of an alternating pattern of a plurality of groups of 2'-modified nucleotides linked by a single unmodified nucleotide, wherein the modified nucleotide on the first stretch is complementary to an unmodified nucleotide on the second stretch. Additionally, the claims are drawn to a ribonucleic acid molecule comprising a double stranded structure having a first and second strand comprising a first and second stretch of nucleotides each comprising a pattern of modifications wherein a 2'-modified nucleotide is linked to a non-modified nucleotide and wherein the modified nucleotide on one strand is complementary to a non-modified nucleotide on the other strand. The claims are further limited wherein the nucleotides are linked to phosphodiester bonds, each strand comprise 15 or more nucleotides, 17-23 or 18-23 nucleotides in length, wherein the RNA molecule is blunt ended on one or both strands, wherein the 2' modifications is from a group as listed in claims 16 and 39, wherein the first nucleotide of each strand or the last nucleotide of each strand is 2'-modified and a pharmaceutical composition comprising said double stranded ribonucleic acid.

McSwiggen et al. teach double stranded RNA comprising a sense and an antisense strand capable of silencing expression of a target gene (see paragraph 0016).

McSwiggen et al. teach specific embodiments of introduction of chemically modified nucleotides in numerous positions throughout the RNA strands and teach such modified dsRNA provide a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules (see paragraph 0037). McSwiggen et al. teach various motifs, configuration and ways of designing dsRNA comprising various chemical modifications and teach specific embodiments wherein the dsRNA comprises about 19-25 nucleotides and said dsRNA can optionally comprise 1-3 nucleotides at the 3' terminus (see paragraph 0035). McSwiggen et al. teach the dsRNA can comprise chemical modifications on one or both strands and teach 1 or more nucleotides on each strand can comprise such modifications comprising phosphodiester internucleoside linkages or 2'-deoxy, 2'-O-methyl, and/or 2'-fluoro modifications (see paragraphs 0174 and 0051-0059). McSwiggen et al. do not specifically teach an embodiment of a dsRNA comprising patterns of a plurality of alternating 2' modified and unmodified nucleotides wherein each group is linked by a single unmodified nucleotide. However, McSwiggen et al. clearly recognize the importance of incorporating 2'- modifications, such as 2'-O-methyl into dsRNA to enhance the stability of said molecule.

Tuschl et al. teach a double stranded RNA, 19-25 nucleotides in length and teach the dsRNA is least 85% complementary and more preferably 100% complementary to the target and that the dsRNA are capable of mediating degradation of homologous RNAs (see paragraph 0017-0019). Tuschl et al. teach dsRNA having blunt ends are capable of mediating interference of gene expression and found dsRNA comprising overhangs on at least one strand are also capable of mediating interference (see Figure

11). Tuschl et al. additionally teach dsRNA molecules may contain nucleotides that are be modified at the 2' position of the ribose sugar. Preferred modifications are listed in paragraph 16 and include 2'-O-alkyl modifications and 2' fluoro modifications. Specific embodiments of modified siRNAs are taught at paragraph 166 and Fig. 14, which describe and show results obtained with 2' modified siRNAs and teach siRNA comprising minimal modifications retain RNAi activity and further teach modification of the entire double stranded RNA with 2'-O-methyl or 2'-deoxy is not well tolerated. Tuschl et al. teach compositions comprising said double stranded RNA molecule and a pharmaceutically acceptable carrier (see paragraphs 0031-0033) and teach a cell or organism comprising said double stranded RNA molecule (see paragraphs 0029 and 0040 and 0043).

Tuschl et al. do not explicitly teach the optimum number and placement of 2'-sugar modifications such that siRNA activity is retained and do not specifically teach a siRNA comprising alternating pattern of 2' modified and unmodified oligonucleotides. However, Tuschl et al. clearly recognize and teach that 2'-modifications enhance the nuclease stability of siRNA molecules and that more extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi. Thus, Tuschl et al. appear to recognize that certain chemical modification of the 2'-OH results in enhanced nuclease resistance as well as modulation of RNAi activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a double stranded RNA molecule comprising 2' modified nucleotides, as taught by McSwiggen et al. and Tuschl et al. and further it would have

been obvious and a matter of routine experimentation to use the general conditions of incorporating various chemical modification in various configurations, as taught by McSwiggen et al. to discover the optimal number and placement of 2'-sugar modifications in any dsRNA molecule, such that the resulting dsRNA molecule was endowed with maximum stability and functionality.

One would have been motivated to test all possibilities and configurations of 2' modified and unmodified nucleotides in one or both strands because it was well known in the art that incorporation of known modifications, such as 2'-O-methyl for example, impart increased stability and functionality in any RNA molecule, such as a dsRNA. MPEP 2144.05 states in part that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Moreover, because Tuschl et al. teach a dsRNA comprising eight 2'-O-methyl modified nucleotides had RNAi activity and fully modifying all 42 nucleotides with 2'-O-methyl abolished RNAi activity, one would have been motivated to search for the optimum number and placement of the 2' modifications within this range by routine experimentation to see how well the modifications were tolerated with respect to stability and functionality of the dsRNA. Because there is a finite number of identified and predictable configurations of 2' modified and unmodified nucleotides known to impart increased stability and functionality in dsRNA as taught by Tuschl et al., one of ordinary skill in the art would have been motivated to incorporate modifications in various

configurations with a reasonable expectation of success at finding a functional motif with increased stability. Furthermore, it would have been routine to one of skill in the art to test these known modifications in various configurations to identify a dsRNA with increased stability and functionality, such as modifying only the first strand of the dsRNA while the strand is unmodified, or modifying every other nucleotide on each strand, for example. Further, since dsRNAs are taught by Tuschl et al. as being useful in cell culture and in whole organisms for elucidating gene function and for therapeutic use and since the chemical modifications of dsRNA are taught by McSwiggen et al. as being capable of improving cellular uptake and stability of dsRNA, one would therefore be motivated to chemically enhance the dsRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene.

One would have a reasonable expectation of success given that McSwiggen et al. teach numerous configurations and motifs comprising 2' modified and unmodified nucleotides in various patterns that were capable of eliciting RNAi. Further, one would have expected success at incorporating the chemical modifications into a dsRNA given Tuschl et al. teach how to make and use virtually any dsRNA to any gene provided the target sequence is known. One of skill in art would have had a reasonable expectation of success at identifying dsRNA comprising an alternating pattern of 2' modified and unmodified nucleotides on one or both strands of RNA from the finite number of possible modifications of a dsRNA taught by Tuschl et al. that retain RNAi activity.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 12-13, 15-17, 19, 29, 31-32 and 34-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al. (U.S. Patent No. 5,955,589), Damha et al. (US 2005/014535) and Tuschl et al. (of record, PTO 892 filed 01/12/2006).

The instant claims are drawn to a double stranded ribonucleic acid molecule wherein the first strand is complementary to a target molecule, the second strand is complementary to a said first strand, wherein each strand comprises a stretch of alternating single 2'-modified and unmodified nucleotides. The claims are further drawn to a double stranded ribonucleic acid molecule comprising a first and second strand comprising a first and second stretch of nucleotides wherein each stretch consists of an alternating pattern of a plurality of groups of 2'-modified nucleotides linked by a single unmodified nucleotide, wherein the modified nucleotide on the first stretch is complementary to an unmodified nucleotide on the second stretch. Additionally, the claims are drawn to a ribonucleic acid molecule comprising a double stranded structure having a first and second strand comprising a first and second stretch of nucleotides each comprising a pattern of modifications wherein a 2'-modified nucleotide is linked to a non-modified nucleotide and wherein the modified nucleotide on one strand is complementary to a non-modified nucleotide on the other strand. The claims are further limited wherein the nucleotides are linked to phosphodiester bonds, each strand

comprise 15 or more nucleotides, 17-23 or 18-23 nucleotides in length, wherein the RNA molecule is blunt ended on one or both strands, wherein the 2' modifications is from a group as listed in claims 16 and 39, wherein the first nucleotide of each strand or the last nucleotide of each strand is 2'-modified and a pharmaceutical composition comprising said double stranded ribonucleic acid.

Cook et al. teach antisense oligonucleotides comprising alternating segments of 2' modified nucleotides and unmodified nucleotides called gapmers or gapped antisense oligonucleotides (see abstract). Cook et al. found that substituting the 2' position on nucleotides increased the binding affinity of the antisense to that target gene and enhanced inhibition of expression (see column 8). Cook et al. teach each nucleotide can be linked with phosphodiester bonds (see Tables 3 and 4 and column 17). Cook et al. do not specifically teach antisense oligonucleotides with alternating 2' modified and unmodified nucleotides and do not teach double stranded oligonucleotides comprising patterns of alternating 2' modified and unmodified nucleotides.

Damha et al. teach antisense oligonucleotides with alternating segments of modified and unmodified nucleotides (see paragraphs 0009-0042, especially paragraph 0014). Damha et al. specifically teach an antisense oligonucleotide consisting of alternating modification linked to an unmodified deoxyribonucleotide and teach the first nucleotide can be a 2' modified nucleotide or can be unmodified and teach the last nucleotide in the strand can be a 2' modified nucleotide or an unmodified nucleotide (see paragraphs 0033-0034). Damha et al. teach the nucleotides can be linked with various internucleoside linkages, such as phosphodiester (see paragraph 0018) and

teach 2' modifications such as methoxy and fluoro (see paragraph 0042). Damha et al. unexpectedly discovered antisense oligonucleotides consisting of this pattern of alternating segments of modified and unmodified nucleotides were able to elicit gene inhibition more efficiently than antisense oligonucleotides without this alternating pattern (see paragraph 0111).

Tuschl et al. teach a double stranded RNA, 19-25 nucleotides in length and teach the dsRNA is least 85% complementary and more preferably 100% complementary to the target and that the dsRNA are capable of mediating degradation of homologous RNAs (see paragraph 0017-0019). Tuschl et al. teach dsRNA having blunt ends are capable of mediating interference of gene expression and found dsRNA comprising overhangs on at least one strand are also capable of mediating interference (see Figure 11). Tuschl et al. additionally teach dsRNA molecules may contain nucleotides that are be modified at the 2' position of the ribose sugar. Preferred modifications are listed in paragraph 16 and include 2'-O-alkyl modifications and 2' fluoro modifications. Specific embodiments of modified siRNAs are taught at paragraph 166 and Fig. 14, which describe and show results obtained with 2' modified siRNAs and teach siRNA comprising minimal modifications retain RNAi activity and further teach modification of the entire double stranded RNA with 2'-O-methyl or 2'-deoxy is not well tolerated. Tuschl et al. teach compositions comprising said double stranded RNA molecule and a pharmaceutically acceptable carrier (see paragraphs 0031-0033) and teach a cell or organism comprising said double stranded RNA molecule (see paragraphs 0029 and 0040 and 0043).

Tuschl et al. do not explicitly teach the optimum number and placement of 2'-sugar modifications such that siRNA activity is retained and do not specifically teach a siRNA comprising alternating pattern of 2' modified and unmodified oligonucleotides. However, Tuschl et al. clearly recognize and teach that 2'-modifications enhance the nuclease stability of siRNA molecules and that more extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi. Thus, Tuschl et al. appear to recognize that certain chemical modifications of the 2'-OH results in enhanced nuclease resistance as well as modulation of RNAi activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a double stranded RNA molecule comprising 2' modified nucleotides, as taught by Tuschl et al. and further it would have been obvious and a matter of routine experimentation to use the general conditions of incorporating alternating segments of modified and unmodified nucleotides, as taught by Cook et al. and Damha et al. to discover the optimal number and placement of 2' modifications in any dsRNA molecule, such that the resulting dsRNA molecule was endowed with maximum stability and functionality.

One would have been motivated to test all possibilities and configurations of 2' modified and unmodified nucleotides in one or both strands because it was well known in the art that incorporation of known modifications, such as 2'-O-methyl for example, impart increased stability and functionality in any inhibitor nucleotides, such as a dsRNA. MPEP 2144.05 states in part that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable

ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Further, given that Cook et al. teach oligonucleotide gapmers comprising alternating segments of 2' modified that flank a segment of unmodified nucleotides and given that Damha et al. unexpectedly found that an antisense oligonucleotide comprising alternating modified and unmodified nucleotides increase target specificity, one would have clearly been motivated to create a dsRNA with one or both strands comprising this alternating pattern of 2' modified and unmodified nucleotides for the purpose of increasing the dsRNA molecules target specificity and increased nuclease stability. Moreover, because Tuschl et al. teach a dsRNA comprising eight 2' modified nucleotides had RNAi activity and a fully 2'-O-methyl modified dsRNA having all 42 nucleotides modified abolished RNAi activity one would have been motivated to search for the optimum number and placement of the 2' modifications in this range by routine experimentation to see how well the modifications were tolerated with respect to stability and functionality of the dsRNA.

Because both Cook et al. and Damha et al. identify alternating patterns of modified and unmodified nucleotides in antisense oligonucleotides and because Tuschl et al. teach dsRNA comprising at least eight 2' modified nucleotides were capable of eliciting RNAi while fully modified dsRNA comprising 42 nucleotides, there is a finite number of identified and predictable configurations of 2' modified and unmodified nucleotides such that one of ordinary skill in the art would have been motivated to incorporate such patterns of modifications with a reasonable expectation of success and

it would have been routine to one of skill in the art to test these known patterns of modifications to identify a dsRNA with increased stability and functionality. Further, since dsRNAs are taught by Tuschl et al. as being useful in cell culture and in whole organisms for elucidating gene function and therapeutic use one would therefore be motivated to chemically enhance the dsRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any siRNA to any gene provided the target sequence is known. Further one would have expected incorporation of alternating patterns of modified and unmodified nucleotides as taught by Cook et al. and Damha et al. as this ability to incorporate modifications and testing such modifications is routine to one of skill in the art. One of skill in art would have had a reasonable expectation of success at creating a dsRNA comprising an alternating pattern of 2' modified and unmodified nucleotides on each strand of said RNA from the finite number of possible modifications of a dsRNA taught by Tuschl et al. that retain RNAi activity.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant' Arguments

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 11-16 and 21-23 under 35 U.S.C. 102(b) as being anticipated by Crooke et al. (cited on PTO Form 892 filed 01/12/2006) is

withdrawn in view of the new grounds of rejection above. Therefore response to Applicant's arguments filed 09/07/2007 is obviated.

The rejection of record of claims 11-19, 21-23, 25-27, 29 and 31-33 under 35 U.S.C. 102(e) as being anticipated by McSwiggen et al. (cited on PTO Form 892 filed 01/12/2006) was not addressed by Applicant but is withdrawn in view of the new grounds of rejection above.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 11-23, 25-27, 29 and 31-33 under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (cited on PTO Form 892 filed 01/12/2006) in view of Holen et al. (Nucleic Acids Research 04/30/2002) is withdrawn in view of the new grounds of rejection above. Therefore response to Applicant's arguments filed 09/07/2007 is obviated.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Examiner
Art Unit 1635